The effects of intravenous insulin infusions on early mortality for patients with acute coronary syndromes who present with hyperglycaemia; a matched propensity analysis using data from the MINAP database 2008-12.

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Word count 2991

Abstract

Importance. Although national guidelines recommend the use of intravenous insulin to control hyperglycaemia in acute coronary syndromes, there is limited evidence of survival benefit from this treatment.

Objective To determine whether the use of intravenous insulin infusions to control admission hyperglycaemia (>=200 mg/dl.) is associated, in contemporary clinical practice, with survival benefit when compared to patients receiving routine care.

Design. We used matched propensity analysis to examine observational data from a large national database for first admissions with acute coronary syndrome. We matched 5974 patients having intravenous infusions with the same number having routine care from a total cohort of 23506 patients with an admission glucose >=200 mg/dl who had either type 2 diabetes or were not known to have diabetes at admission to hospital. We separately examined the effect of insulin infusions for ST elevation and non-ST segment elevation infarctions, and for type 2 diabetes and those without known diabetes.

Setting Acute admissions to 220 hospitals in England and Wales between January 2008 and March 2012 who had a final diagnosis of acute coronary syndrome.

Outcome Survival to 7 days following admission.

Results Survival benefit from the use of intravenous insulin infusions was seen only for ST elevation infarctions not known to have diabetes; adjusted hazard ratio (HR) 0.77 (95% confidence interval 0.64 - 0.92), p=0.005. ST elevation infarctions with existing type 2 diabetes who received intravenous infusions had similar outcomes to routine care, HR 0.99 (95% CI 0.80 - 1.23), p=0.931. For non-ST elevation infarctions routine care was associated with significantly better adjusted 7 day survival than intravenous infusions regardless of diabetes status; for those without known diabetes, HR 1.50 (95% CI 1.04 - 2.16) p=0.029, and for those with type 2 diabetes, HR 1.35 (95% CI 1.08 - 1.70), p=0.010.

Conclusion In contemporary clinical practice, the use of intravenous insulin infusions to treat hyperglycaemia in acute coronary syndromes is associated with significant survival benefit only for those with ST segment elevation infarctions who are not known to have diabetes. Non-ST segment elevation infarctions show significant survival benefit from routine care compared with intravenous insulin infusions.

Introduction

In acute coronary syndrome (ACS), higher levels of blood glucose at admission are associated with lower survival rates,[1-3] while early falls in those presenting with raised blood glucose are associated with improved survival.[4] Normalization of glucose after admission is associated with better survival in hyperglycaemic patients with ACS whether or not they are treated with insulin.[5] However, randomised studies that have examined the impact on mortality of lowering blood glucose with intravenous insulin infusions (IVII) have presented conflicting results.[6-8] The evidence for benefit rests on a single randomised study that did not achieve its primary end point,[6] while other randomised studies using IVII have failed to show survival benefit.[7,8]

Despite the limited evidence base, national clinical guidelines currently recommend IVII for ACS presenting with hyperglycaemia.[9-13] However, there is presently no evidence that survival benefit from use of IVII applies across the spectrum of ACS, nor that responses of those with or without a prior diagnosis of diabetes are similar. The current limited use of insulin in ACS with hyperglycaemia reflects the weakness of the evidence base[14].

We used data from the National Audit of Myocardial Ischaemia Project (MINAP) database[15] to examine the effect of IVII in patients with ACS presenting with glucose >=200 mg/dl. in the context of contemporary clinical practice. We separately examined survival benefit from the use of IVII compared to routine care for those not known to have diabetes and for those with type 2 diabetes, and also for myocardial infarction presenting with ST segment elevation (STEMI) and without ST segment elevation (nSTEMI). In order to assess the immediate effect of IVII, and to avoid any effect of intense post-discharge glycaemic control, we examined survival to seven days following admission.

Methods

The MINAP database contains details of ACS admissions to hospitals in England and Wales.[15] The database records information on patient co-morbidity and management for both STEMI and nSTEMI, and for the purposes of this study provided information on admission blood glucose, type of diabetes, and pre-hospital and inpatient management of hyperglycaemia. Fully anonymised data were extracted from the MINAP database, and included records from all hospitals in England and Wales (n=220) accepting emergency admissions between January 2008 and March 2012. The United Kingdom Office of National Statistics provided mortality status.

Patient cohort. We examined management and outcomes for first admissions having a final diagnosis of troponin positive ACS, either with or without ST segment elevation, and who had an admission blood glucose within the range 200-900 mg/dl. (for mmol/l multiply by 0.055). ACS were categorised as STEMI and nSTEMI based on biomarker and electrocardiographic criteria. Patients had either pre-existing type 2 diabetes treated with dietary restriction, or oral medication, with or without additional subcutaneous insulin, or were not known to have diabetes at the time of admission. Treatment allocation to IVII or routine care was determined by the attending physician. Insulin infusions were prescribed according to local practice, and were not standardised. Blood glucose was measured either by bedside analysis or in the laboratory.

Statistical analysis We examined distributions of baseline variables of patient characteristics, cardiovascular risk factors, and glucose level and medications at hospital admission between patients receiving routine care and IVII. Categorical variables were summarised using frequencies and percentages, and a χ^2 test was used to compare differences between two groups. We used the median and interquartile range (IQR) for continuous variables, with the Mann-Whitney test for differences. As preliminary analyses demonstrated significant differences in clinical characteristics between those receiving IVII and those receiving routine care, a multivariate logistic regression model was developed, based on important clinical features or having statistical significance on univariate analysis ($p<0.001$), to calculate the probability of being treated with IVII using the following

variables: age, gender, admission blood glucose as a categorical variable, (200-217, >217-253, >253 – 290, >290 – 326, >326 – 362, >362 – 900 mg/dl.), type of infarction (nSTEMI/STEMI), a previous history of myocardial infarction, hypertension, hyperlipidaemia, chronic renal failure (creatinine >200 micromol/l), chronic obstructive airways disease, peripheral vascular disease, diabetes status, prescription of a loop diuretic (as a surrogate for development of heart failure during admission[16]), use of angiography,[17] and primary reperfusion strategy for STEMI (thrombolytic treatment, primary percutaneous coronary intervention (pPCI), or no reperfusion treatment). We matched the propensity score to within 0.01 between patients having IVII and routine care using 1:1 matching criteria. Multivariate adjusted Cox regression models were then used to examine the effects of IVII on survival to 7 days after admission for those with STEMI and nSTEMI, and for patients with and without diabetes. The following covariates were also used in these models; treatment before admission with aspirin, angiotensin converting enzyme (ACE) inhibitors or receptor blockers, beta blockers, thienopyridines and statins, previous PCI, previous coronary artery bypass grafting, and current cigarette smoking. In the adjustment analysis any missing data amongst the variables were coded and included in analysis. We tested for an interaction effect between IVII and routine care on mortality for STEMI and nSTEMI, and for those with diabetes and those not known to have diabetes, using a 2-sided p value, and calculated the ratio of hazard ratios for survival benefit with IVII.[18] All analyses in this study were performed in the SAS statistical program (SAS Version 9.2, SAS Institute Inc, Cary, NC).

Results

From 36738 records of patients having an admission glucose in the range >= 200 mg/dl. to <=900 mg/dl, we identified 23506 patients who had either type 2 diabetes or were not known to have diabetes on admission to hospital, and who had an explicit management strategy for hyperglycaemia. 70.3% (16520) received routine care and 29.7% (6986) had IVII.(figure 1) Of 23506, 51.2% (12041) had type 2 diabetes and 48.8% (11465) were not known to have diabetes at admission; 43.5% (10216) had STEMI, and 56.5% (13290) nSTEMI. While IVII was used for 29.7% patients overall, it

was used substantially more frequently for those with existing diabetes, 41.6% (5007 of 12041) than those not known to have diabetes, 17.1% (1979 of 11465).

Table 1 shows patient characteristics for the whole cohort. Those having IVII and those having routine care differed in several important respects. Those receiving IVII were significantly younger, and were more likely to be male. They also had a higher median admission glucose; 286 mg/dl against 235 mg/dl. Those having STEMI were also more likely to receive insulin than those with nSTEMI. Data on other clinical characteristics appear in on-line data table e1. In view of the important differences between those having IVII and routine care, and the substantially greater use of IVII for those with known diabetes, we used matched propensity analysis to compare survival at 7 days following admission. Of 6986 patients having IVII 5974 (85.5%) were matched 1:1 with patients having routine care. The clinical characteristics of the matched cohort are shown in table 2. There were no significant differences in clinical characteristics, except that a higher proportion of patients with type 2 diabetes patients had routine care, and a higher proportion were using beta blockers before admission.

Survival outcome at 7 days. The 7 day mortality for all STEMI was 14.6%, (819 of 5608); for those with type 2 diabetes it was 11%, (338 of 3081) and for those not known to have diabetes 19%, (481 of 2527). The 7 day mortality for nSTEMI was 7%, (444 of 6340); for those with type 2 diabetes it was 6.1%, (311 of 5111), and for those not known to have diabetes it was 10.8%, (133 of 1229). For STEMI overall, IVII was associated with a 15% lower adjusted mortality compared with routine care; for patients without known diabetes there was a 23% lower mortality, while for those with known diabetes there was no significant difference.(table 3) In contrast to STEMI, use of IVII for nSTEMI was associated with increased mortality, regardless of diabetes status. After adjustment, the HR for 7 day survival favoured routine care over IVII; HR 1.42, $p<0.001$, for type 2 diabetes HR=1.35, $p<0.001$, and for those not known to have diabetes HR=1.5, $p=0.029$. An interaction analysis showed that the survival benefit effect of IVII was significantly more powerful for those with STEMI compared to nSTEMI; the ratio of hazard ratios (RRR) was 0.60 (0.47-0.76) overall,

0.51 (0.34-0.77) in patients without known diabetes and 0.73 (0.54-1.01) in patients with known diabetes.

The impact of primary reperfusion strategy on outcome for STEMI. As mortality differed substantially between those having thrombolytic treatment (16.4%) , primary PCI (9.6%) and those not having reperfusion treatment, (20.2%), the impact of IVII was examined for each group. For those with established type 2 diabetes the HR for 7 day survival was similar for IVII and routine care in each reperfusion subgroup, in the range 0.89–1.09, p>0.05. (table 4). For those not known to have diabetes, IVII was associated with marked survival benefit for those having thrombolytic treatment; HR 0.68, p=0.019 and for primary PCI; HR 0.71, p=0.047. In those not receiving reperfusion treatment, IVII did not show any survival benefit over routine care; HR 0.93, p=0.933.

Sensitivity analyses We performed a sensitivity analysis excluding those patients who had any missing data in any of the variables used for adjustment. The number of patients in the analysis was 8746, 73.2% of 11948 propensity matched patients. There were no significant differences in those included between between IVII and routine care groups, and analyses showed similar overall results to those in tables 3 and 4.(tables e2 and e3). However, the benefits of routine care on survival seen for nSTEMI were slightly attenuated, and were no longer significant in the subgroups of patients with and without diabetes. A small proportion of those with diabetes (5.2%) received insulin with oral medication prior to admission. We found that excluding this group from analysis also had no significant impact on the overall results. (table e4)

Discussion

This study using data from a national registry of ACS showed that, as used in contemporary clinical practice, survival benefit from the use of insulin infusions for hyperglycaemia did not extend to all ACS, but was limited to STEMI. This resulted from a 23% better adjusted survival outcome at seven

days for STEMI without known diabetes, while for STEMI with known type 2 diabetes survival for those having IVII and routine care was the same. For nSTEMI, routine care was associated with better outcome than IVII. The difference in response to IVII between STEMI and nSTEMI was marked; an interaction analysis showed the survival benefit effect from IVII was significantly more powerful for those having STEMI than for nSTEMI.

There is a strong patho-physiological basis for the toxicity of hyperglycaemia in ACS, based on oxidative stress,[19,20] enhanced platelet activation and thrombin formation,[21] and impaired response to antiplatelet drugs [22], which makes timely glucose control with insulin a plausible clinical approach. However, despite this, the evidence for survival benefit from the use of insulin to normalise raised blood glucose is based on a single randomised study that examined the combined effects of intravenous insulin in hospital and three months of intense post-discharge glycaemic control.[6] It remains uncertain to what extent the reported benefit at one year was due to intense glycaemic control after discharge, and how much was due to the in-hospital insulin. Two other studies failed to show survival benefit for IVII.[7,8] A recent randomised open label study using infarct size as an end point in a mixed population of STEMI (85%) and nSTEMI; type 2 diabetes (10 %), and those not known to have diabetes, failed to show a significant difference in infarct size between those randomised to intensive glycaemic control with insulin and those having routine care, despite those having insulin achieving significantly lower blood glucose values.[23] Evidence for survival benefit from IVII is therefore limited to a small observational study from a cohort without prior diabetes presenting with a blood glucose >= 200 mg/dl.[24] This showed findings consistent with the present study; a difference in effect of IVII between STEMI and nSTEMI, with survival benefit seen only for STEMI.

In addition to the evidential limitations, the management of ACS has changed greatly since publication of DIGAMI 1 in 1995 and this may influence the present response to IVII.[6] Primary PCI, accompanied by use of increasingly effective anti-platelet and anti-thrombotic medication is now the reperfusion treatment of choice for STEMI,[25] while for nSTEMI angiography and, where appropriate, coronary intervention are now mandated. Furthermore, the extensive use of angiotensin receptor

inhibitors, and statins prior to admission may favourably influence early outcome independently of any intervention with insulin, by their effects on the no-reflow phenomenon.[26, 27] These interventions may be sufficiently powerful to attenuate any effects of IVII, especially for nSTEMI where seven day mortality was one half of that seen for STEMI in this study.

For STEMI in patients not known to have diabetes the effect of IVII was powerful, and was similar for those having thrombolytic treatment (HR 0.68 p = 0.019) and primary PCI (HR 0.71, p=0.047). However, in patients with STEMI who did not receive primary reperfusion treatment there was no survival benefit of IVII over routine care. This heterogeneous group includes those who do not receive reperfusion treatment because of co-morbidities, those who present late, and those who are found to be unsuitable for, or did not require, an immediate intervention. They represented 27% of all STEMI in this study, and it is possible that subsets within this group may yet benefit from IVII. For STEMI in patients with type 2 diabetes, IVII was associated with similar outcomes to routine care, although the confidence limits did not exclude the possibility of a small benefit. While the routine use of IVII would not appear justified for this group, these findings should not inhibit the use of IVII at higher levels of admission glucose and where hyperglycaemia may be associated with more general metabolic disturbance.

For nSTEMI, whether or not patients had a prior diagnosis of type 2 diabetes, these analyses favoured routine care. These findings are similar, though more marked, to those in the DIGAMI 2 study[7], where routine care for type 2 diabetes showed an early trend towards lower mortality when compared to IVII. The potentially adverse effects of hypoglycaemia may be relevant.[28-30] The use of insulin infusions for severely ill patients in the ITU setting, although not necessarily applicable to acute coronary ischaemia, initially suggested a target glucose range of 80-110 mg/dl,[31] until concern about the adverse effects of hypoglycaemia on mortality encouraged a relaxation of this target.[32] However, if an intensive glucose target was adopted by clinicians using DIGAMI regime, where hypoglycaemia rates of 15% were reported,[6] this may have led to adverse outcomes, although more recent work, in the context of a clinical trial, has reported that lower rates of hypoglycaemia can be achieved while using a target range of 80-110 mg/dl.[23]

These analyses confirm that those having type 2 diabetes, of whom the majority were taking oral medication, had a lower mortality than those not known to have diabetes. While the mechanism whereby oral hypoglycaemic drugs favourably affect outcome may simply be by providing timely glycaemic control during the critical early phase of infarction, metformin, the recommended first-line oral medication in American, European,[33] and United Kingdom guidelines,[34] has additional beneficial metabolic effects.[35] In patients with type 2 diabetes undergoing primary PCI for STEMI, pre-admission use of metformin was associated with a lower frequency of the no-reflow phenomenon.[36] For those with type 2 diabetes the present findings support the continued use of oral therapy, particularly metformin, during the acute phase of infarction, and are consistent with the wider beneficial cardiovascular effects demonstrated for metformin by the UKPDS collaborators.[37]

Despite having a lower mortality than those without known diabetes, those with known diabetes were more likely to receive IVII in this study. Use of IVII was greater in those with type 2 diabetes and STEMI, 54%, a group where we were unable to show survival benefit, than for STEMI without a prior diagnosis of diabetes where IVII were used for only 22%. Even more limited use of intravenous insulin has recently been reported from the United States.[14] This may reflect awareness amongst clinicians of the paucity of the evidence base, and continuing concerns about the potential adverse effects of IVII. Scepticism for the role of IVII by clinicians appears to be justified on the basis of the present findings.

Limitations. This large database inevitably had missing data. After excluding patients who had missing data in any of the variables used for adjustment, we found that the effects of IVII were broadly similar when compared to analyses that included all matched patients, although for nSTEMI the survival benefit of routine care for subsets with and without prior diabetes was slightly attenuated and no longer statistically significant. (tables e2, e3 on-line data). In addition, the timing of the insulin infusion in relation to the onset of symptoms, which may be very important, was not routinely recorded. However, from 2010 onwards this was recorded in the MINAP database in a group of patients with hyperglycaemia having ACS (n= 776) in 40 hospitals as part of the evaluation of a new

intravenous insulin regime and provides an indication of contemporary practice (MINAP data on file); the median delay from arrival in hospital to insulin infusion was 4.3 h (IQR 2.6 - 7.7 h). We also considered the risk of survivor bias from deaths occurring very early after admission, before insulin treatment could be started. However, in previous work we have shown that when deaths within 24 h. of admission were excluded, 7 and 30 day adjusted outcomes were only slightly attenuated.[24.] Finally, we do not have a record of the frequency of hypoglycaemic episodes which may of relevance to mortality outcome for nSTEMI.

Conclusion. We have shown that responses to IVII are not consistent between STEMI and nSTEMI, and that responses to IVII by those known to have diabetes differ from those without known diabetes. It is important that any future work to determine the role of IVII should recognise these differences.

Acknowledgements

Author contributions. Dr Birkhead conceived this study, Drs Birkhead and Chen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Chen performed the statistical analyses. Dr Weston provided critical input throughout the development of the paper. All authors provided critical evaluation of the final text.

Data Source Data were provided with the agreement of the MINAP Academic Group based at the National Institute for Cardiovascular Outcomes Research (NICOR) 170 Tottenham Court Road London WCI. UK.

Disclosures. John Birkhead, Clive Weston, Adam Timmis and Ruoling Chen have no conflicts of interest to declare.

Funding Source. MINAP is funded through NICOR by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme. HQIP had no part in the design and conduct of the study; in collection, management, analysis, and interpretation of the data, in preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

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Figure legend

Figure 1. Origin of cohort with acute coronary syndrome and admission glucose >=11 mmol/l from which matched propensity groups were derived.

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	Routine care n= 16520	Insulin infusion n= 6986	p value
Patient characteristics			
Age y [a]	74.0 (62.9, 82.1)	70 (59.7, 79)	<0.001
Male gender	10163/16491 (61.6)	4475/6980 (64.1)	<0.001
Admission glucose mg/dl [a,b]	235 (212, 275)	286 (235, 349)	<0.001
nSTEMI	9886/13290 (74.4)	3404/13290 (25.6)	<0.001
STEMI	6634/10216 (64.9)	3582/10216 (35.1)	<0.001
Diabetes status			
Type 2 diabetes	7034/16520 (42.6)	5007/6986 (71.7)	<0.001
Diet control	1316/7034 (18.7)	679/5007 (13.6)	<0.001
Oral medication	5657/7034 (80.4)	3765/5007 (75.1)	<0.001
Oral plus insulin	61/7034 (0.9)	563/5007 (11.2)	<0.001
Not known to have diabetes	9486/16520 (57.4)	1979/6986 (28.3)	<0.001

Table 1. Main clinical characteristics of the whole cohort, n= 23506. [a] median, interquartile range. [b] For mmol/l multiply by 0.055. Bracketed numerals are percentages except where otherwise indicated. Details of other previous medical history, drugs taken before admission, and hospital care, appear in the Appendix table e1.

	Routine care n = 5974	Insulin infusion n=5974	P value
Age, y [a]	71.0 (59.9-80.0)	70.0(59.7-79.0)	0.928
Male gender	3854/5970 (64.6)	3797/5969(64.6)	0.282
Final diagnosis:			
STEMI	2762 (47.6)	2846 (46.2)	0.124
NSTEMI	3212 (52.4)	3128 (53.8)	
Admission Glucose mg/dl [a b]	272 (230, 326)	272 (230, 326)	0.096
Diabetes status			
Not known diabetes	1826 (30.6)	1930 (32.3)	0.040
Type 2 diabetes	4148 (69.4)	4044 (67.7)	
Previous medical status			
Hypertension	3483/5805 (60)	3438/5804 (59.2)	0.401
Hyperlipidaemia	2418/5679 (42.6)	2388/5682 (42.0)	0.553
Previous MI	1379/5803 (23.8)	1384/5799 (23.9)	0.897
Heart Failure	402/5780 (7.5)	399/5783 (6.9)	0.906
Chronic Renal Failure	401/5771 (6.9)	397/5775 (6.9)	0.246
Chronic obstructive pulmonary disease	844/5767 (14.6)	842/5775 (14.6)	0.933
Previous PCI	509/5795 (8.9)	521/5777 (9.0)	0.657
Previous CABG	382/5806 (6.6)	400/5791 (6.9)	0.481
Current cigarette smoking	1482/5560 (26.7)	1452/5595 (26)	0.399
Medication taken before admission:			
ACEI or ARB	2543/5580 (45.6)	2579/5650 (45.6)	0.999
Beta blocker	1787/5589 (32.0)	1698/5653 (30.0)	0.026
Statin	3004/5707 (52.6)	3014/5783 (51.9)	0.578
Aspirin	1568/5745 (27.3)	1647/5774 (28.5)	0.141
Thienopyridine	730/5306 (13.8)	725/5307 (13.7)	0.885
Primary reperfusion for STEMI:			
No primary reperfusion treatment	775/2762 (28.1)	787/2846 (27.7)	0.817
Thrombolytic treatment	796/2762 (28.8)	842/2846 (29.6)	
Primary angioplasty	1191/2762 (43.1)	1217/2846 (42.8)	
Angiography for nSTEMI	1852/2879 (64.3)	1817/2835 (64.1)	0.879
Use of loop diuretic	2357/5688 (41.4)	2379/5683 (41.9)	0.647

Table2. Clinical characteristics of propensity matched groups. Bracketed numerals are percentages except where otherwise indicated. [a] median and interquartile range. [b] To convert mg/dl - mmol/l multiply by 0.055.

	Management strategy	Number of patients	Death within 7 days (%)	Adjusted HR (95% CI)	P value
STEMI (all)	Routine care	2762	451 (16.3)	1	
	Insulin infusion	2846	368 (12.9)	0.85 (0.74 - 0.98)	0.026
With type 2 diabetes	Routine care	1503	175 (11.6)	1	
	Insulin infusion	1578	163 (10.3)	0.99 (0.80 - 1.23)	0.931
Not known to have diabetes	Routine care	1259	276 (21.9)	1	
	Insulin infusion	1268	205 (16.2)	0.77 (0.64 - 0.92)	0.005
nSTEMI (all)	Routine care	3212	186 (5.8)	1	
	Insulin infusion	3128	258 (8.2)	1.42 (1.17 - 1.72)	<0.001
With type 2 diabetes	Routine care	2645	133 (5.0)	1	
	Insulin infusion	2466	178 (7.2)	1.35 (1.08 - 1.70)	0.010
Not known to have diabetes	Routine care	567	53 (9.3)	1	
	Insulin infusion	662	80 (12.1)	1.50 (1.04 - 2.16)	0.029

Table 3. Hazard ratio for 7 day survival for STEMI and nSTEMI. Routine care = 1.

		Management strategy	Number of patients	Death within 7 days (%)	Adjusted HR (95% CI)	p value
Type 2 diabetes	**Thrombolytic treatment**	**Routine care**	305	44 (14.4)	1	
		Insulin infusion	398	44 (11.1)	0.89 (0.55 - 1.42)	0.612
	Primary angioplasty	**Routine care**	684	45 (6.6)	1	
		Insulin infusion	714	41 (5.7)	0.90 (0.57 - 1.43)	0.668
	No primary reperfusion	**Routine care**	514	86 (16.7)	1	
		Insulin infusion	466	78 (16.7)	1.09 (0.79 - 1.49)	0.614
Not known to have diabetes	**Thrombolytic treatment**	**Routine care**	491	114 (23.2)	1	
		Insulin infusion	444	67 (15.1)	0.68 (0.49 - 0.94)	0.019
	Primary angioplasty	**Routine care**	507	87 (17.2)	1	
		Insulin infusion	503	62 (12.5)	0.71 (0.50 - 0.99)	0.047
	No primary reperfusion	**Routine care**	261	75 (28.7)	1	
		Insulin infusion	321	76 (23.7)	0.93 (0.66 - 1.31)	0.933

Table 4. Hazard ratio for 7 day survival for individual primary reperfusion strategies for STEMI. Routine care = 1.

Supplemental material

Previous medical status	Routine care n= 16520 (%)	Insulin infusion n= 6986 (%)	p value
Hypertension	8978/16120 (55.7)	4041/6773 (59.7)	<0.001
Cardiac failure	1181/16034 (7.4)	472/6744 (7)	0.33
Chronic obstructive airways disease	2598/16046 (16.1)	959/6732 (14.2)	<0.001
Chronic renal failure	1022/16052 (6.4)	457/6739 (6.8)	0.246
Treated hyperlipidaemia	5538/15815 (35)	2860/6615 (43.2)	<0.001
Myocardial infarction	3891/16090 (24.2)	1595/6771 (23.6)	0.311
Peripheral vascular disease	727/15844 (4.6)	383/6582 (5.8)	<0.001
CABG	1035/16107 (6.4)	458/6719 (6.8)	0.341
PCI	1307/16075 (8.1)	616/674 (39.1)	0.013
Current cigarette smoking	3856/15335 (25.1)	4475/6980 (26.9)	0.008
Admission drugs			
ACEI/ARB	6411/15459 (41.5)	3020/6599 (45.8)	<0.001
Aspirin	4259/15835 (26.9)	1897/6746 (28.1)	0.059
beta blocker	4695/15835 (30.3)	1961/6605 (29.7)	0.356
statin	7342/15806 (46.5)	3522/6751 (52.2)	<0.001

thienopyridine	1872/14722 (12.9)	835/6180 (13.5)	0.196
In hospital management			
Primary angioplasty	3162/6634 (47.7)	1457/3582 (40.7)	<0.001
Thrombolytic treatment	1511/6634 (22.8)	1157/3582 (32.3)	<0.001
No reperfusion	1961/6634 (29.6)	968/3582 (27)	<0.001
Angiography for nSTEMI	5069/8834 (57.4)	2051/3141 (65.3)	<0.001
In hospital loop diuretic use	6094/15575 (39.1)	2874/6665 (43.1)	<0.001

Table e1. Other clinical characteristics of the whole cohort (n=23506).

	Management strategy	Number of patients	Death within 7 days, %	Adjusted HR 95% CI	P value

STEMI (all)	Routine care	259/1942	13.3	1.00	
	Insulin infusion	221/2030	10.9	0.79 (0.66-0.95)	0.012
With type 2 diabetes	Routine care	104/1058	9.8	1.00	
	Insulin infusion	100/1136	8.8	0.90 (0.68-1.19)	0.466
Not known to have diabetes	Routine care	155/884	17.5	1.00	
	Insulin infusion	121/894	13.5	0.70 (0.55-0.89)	0.004
nSTEMI (all)	Routine care	127/2424	5.2	1.00	
	Insulin infusion	157/2350	5.7	1.31 (1.03-1.66)	0.026
With type 2 diabetes	Routine care	90/2017	4.5	1.00	
	Insulin infusion	103/1853	5.6	1.29 (0.97-1.71)	0.085
Not known to have diabetes	Routine care	37/407	9.1	1.00	
	Insulin infusion	54/497	10.7	1.27 (0.83-1.96)	0.275

Table e2 Sensitivity analysis. Patients without any missing covariate data. Hazard ratio for 7 day survival for STEMI and nSTEMI. Routine care = 1.

		Management strategy	Number of patients	Death within 7 days (%)	Adjusted HR	p
Type 2 diabetes	**Thrombolytic treatment**	**Routine care**	24/215	11.2	1.00	
		Insulin infusion	29/294	9.9	0.94 (0.52-1.68)	0.833
	Primary angioplasty	**Routine care**	24/477	5.0	1.00	
		Insulin infusion	25/509	4.9	0.85 (0.47-1.52)	0.575
	No primary reperfusion	**Routine care**	56/366	15.3	1.00	
		Insulin infusion	46/333	13.8	0.92 (0.61-1.38)	0.896
Not known to have diabetes	**Thrombolytic treatment**	**Routine care**	60/335	17.9	1.00	
		Insulin infusion	35/307	11.4	0.57 (0.37-0.88)	0.011
	Primary angioplasty	**Routine care**	54/366	14.8	1.00	
		Insulin infusion	39/367	10.6	0.61 (0.40-0.94)	0.026
	No primary reperfusion	**Routine care**	41/183	22.4	1.00	
		Insulin infusion	47/220	21.4	1.03 (0.67-1.61)	0.883

Table e3 Sensitivity analysis. Patients without any missing covariate data. Hazard ratio for 7 day survival for individual primary reperfusion strategies for STEMI. Routine care = 1.

	Management strategy	Number of patients	Death within 7 days	Adjusted HR (95% CI)	P value
STEMI (all)	Routine care	488/2745	16.3	1.00	
	Insulin infusion	361/2713	13.3	0.87 (0.75 – 0.99)	0.048
STEMI with type 2 diabetes	Routine care	172/1486	11.6	1.00	
	Insulin infusion	156/1445	10.8	1.04 (0.83 – 1.30)	0.751
nSTEMI (all)	Routine care	183/192	5.8	1.00	
	Insulin infusion	243/2810	8.6	1.44 (1.19 – 1.75)	<0.001
nSTEMI with type 2 diabetes	Routine care	132/2625	5.0	1.00	
	Insulin infusion	163/2148	7.6	1.37 (1.09 – 1.74)	0.008

Table e4. Sensitivity analysis after exclusion of patients with type 2 diabetes (n=624) using subcutaneous insulin with oral Medications before admission. Routine care = 1.